The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

Paper No. 58

UNITED STATES PATENT AND TRADEMARK OFFICE

_____

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

_____

Ex parte
PIERRE H. CHAMBON, DANIEL METZGER, and JOHN WHITE

_____

Appeal No. 1999-1367
Application No. 08/453,998

_____

ON BRIEF[1]

_____

Before WINTERS, WILLIAM F. SMITH, and SCHEINER, Administrative Patent Judges.

WILLIAM F. SMITH, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 4, 10, 11, 13-17, 25, and 27, all the claims remaining in the application.

[1]Appellants requested an oral hearing. The hearing was set for July 12, 2001. On July 9, 2001, appellants filed a request to reschedule the hearing. The request was granted, and the July 12 hearing was vacated. However, in reviewing the case in preparation for the scheduled hearing, it became apparent to the merits panel that a hearing would not be necessary, for the reasons presented below. Therefore the request to reschedule is moot.

Claim 25 is representative of the claims on appeal and reads as follows:[2]

25. A method of preparing a heterologous protein that comprises:

i) transforming a yeast cell with:

a) a first DNA fragment encoding said heterologous protein under control of elements providing for expression of said first DNA fragment in yeast, said elements comprising a higher eukaryotic positive transcription control sequence selected from the group consisting of

a natural ligand responsive element activating sequence or

a variant of a natural ligand responsive element activating sequence which is a palindromic sequence or a repetition of a palindromic sequence and which retains the function of a natural ligand responsive element activating sequence in a test of inducible expression of $-galactosidase in yeast,

that is induced by a higher eukaryotic receptor complexed with a ligand, and

b) a second DNA fragment that is functional in yeast and that encodes said receptor under control of elements providing for expression of said receptor in yeast, wherein said receptor is a natural nuclear receptor selected from the group consisting of

receptors

for steroids or

for retinoids or

for thyroid hormones or

for vitamin D3, and

[2] For clarity we have reproduced the claim in a manner which differs from the record copy in that the clauses are separated and indented.

variants of said receptors which retain the function of said receptors in yeast, wherein said receptor comprises a first fragment that recognizes said ligand and a second fragment that binds to said transcriptional control sequence;

ii) culturing said transformed yeast cell resulting from step (i) in the presence of said ligand completed with the said expressed receptor whereby said transcription control sequence is induced and said heterologous protein is thereby produced; and

iii) isolating said heterologous protein.

The references relied upon by the examiner are:

Evans et al. (Evans) 5,071,773 Dec. 10, 1991
Meyhack et al. (Meyhack) 5,175,105 Dec. 29, 1992

Green et al. (Green) "Human Oestrogen Receptor cDNA: Sequence, Expression and Homology to V-erb-A," Nature Vol. 320 pp. 134-139 (1986)

Green et al. (Green) "A Versatile in Vitro and in Viro Eukaryotic Expression Vector for Protein Engineering," Nucleic Acids Research Vol. 16 No. 1 p.369(1988)

Krust et al. (Krust) " The Chicken Oestrogen Receptor Sequence: Homology with V-erbA and the Human Oestrogen and Glucocorticoid Receptors," The EMBO Journal Vol.5(5) pp. 891-897 (1986)

West et al. (West) "Saccharomyces Cerevisiae GAL1-GAL10 Divergent Promoter Region: Location and Function of the Upstream Activating Sequence $UAS_{G"}$ Molecular and Cellular Biology Vol. 4(11) pp. 2467-2478 (1984)

Martinez et al. (Martinez) " The Estrogen-responsive element as an Inducible enhancer: DNA Sequence requirements and Conversion to a Glucocorticoid-Responsive element," The EMBO Journal Vol. 6(12) pp. 3719-3727 (1987)

Cushing et al. (Cushing) "A Study of the Effects of 17-$-Estradiol on The Growth of Saccharomyces Cerevisiae," Academy of Science Vol. 79 pp.111-116 (1986)

GROUNDS OF REJECTION

Claims 4, 10, 11, 13-17, 25, and 27 stand rejected under 35 U.S.C. 112, second paragraph, as indefinite.

Claims 4, 10, 11, 13, 14, 15, 25, and 27 stand rejected under 35 U.S.C. 103(a). As evidence of obviousness, the examiner cites Cushing, Evans, Green (Nature), Green (Nuc. Acids. Res.), Krust, West, and Martinez.

Claims 15 and 17 stand rejected under 35 U.S.C. 103(a). As evidence of obviousness, the examiner cites Cushing, Evans, Green (Nature), Green (Nuc. Acids. Res.), Krust, West, and Martinez as applied to the claims above, and further cites Meyhack.

We reverse.

BACKGROUND

The claims on appeal involve a method of producing a foreign protein in yeast. The coding sequence for the foreign protein is placed under an inducible expression control. The induction mechanism is adopted from higher eukaryotic cells. A receptor protein is expressed in the cell which has two functional parts: one part which binds a ligand to form a complex, and one part which binds the complex to a specific sequence of DNA. The specific sequence of DNA is termed a responsive element. When the receptor complex binds to a responsive element linked to the foreign protein coding sequence, expression of the foreign protein is induced. See, generally, specification pages 3 and 5. An example of

the receptor protein is the human estrogen receptor “hER”; an example of the responsive element is the chicken vitellogenin estrogen responsive element “ERE”. See, generally, specification pages 7 and 8, and example 1 on pages 10-14.

Definiteness

We begin with the proposition that “the definiteness of the language employed [in a claim] must be analyzed--not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art.” In re Moore, 439 F.2d 1232, 1235, 169 USPQ 236, 238 (CCPA 1971)(footnote omitted).

The Examiner’s answer states that the metes and bounds are indeterminable for that portion of the claimed subject matter directed to "a variant of a natural ligand responsive element activating sequence which is a palindromic sequence or a repetition of a palindromic sequence and which retains the function of a natural ligand responsive element activating sequence in a test of inducible expression of $-galactosidase.” The examiner states (Examiner’s Answer, Page 5 (Paper No. 44)) :

> The application does not disclose any nor do the claims indicate what are or are not the criteria for determining/defining what is or is not a variant of a natural ligand responsive element activating sequence which retains the function of a natural ligand responsive element activating sequence in a test of inducible expression of B-galactosidase (note that the E. coli IacZ DNA would fulfill the requirement as a variation of the original ERE sequence). There is no indication of what bases, which bases in the sequence, nor how many bases are or are not in a variant and which of the functions is the function that is retained...In fact, the instant claim reads on any

element because there is no criterion presented in the specification nor in the claim that defines any line of demarcation of variant and not variant.

The examiner also rejects the claim for failing to describe variants in a manner which excludes natural elements, asserts that all of the variants have the same function as the natural element which is defined by function. The examiner also argues that claim 27 is ambiguous regarding the orientation of repeated elements to each other and to any other elements in the construct. In addition, the examiner argues that "in a test of inducible expression of $-galactosidase" does not state the point of delineation of inducible expression nor how the test makes a variant different from a natural response element.

We disagree. First, it is not necessary for all members of a Markush group to be mutually exclusive; the mere fact that a compound may be embraced by more than one member of a Markush group recited in the claim does not necessarily render the scope of the claim unclear. Ex parte Kristensen,10 USPQ 2d 1701 (Bd. Pat. App & Int. 1989). In regard to confusing variants with natural elements, logic dictates that a variant must vary from a natural element, and therefore the term "variants" does exclude the natural element. We do not agree that the natural ligand responsive elements responsive to steroids, retinoids, thyroid hormones, or vitamin D3 all have the same function, since each type of responsive element binds to a different receptor protein. The language of claim 25 states that the variants used in the claim must "retain the function of a natural ligand responsive element activating sequence" in a particular test format, "inducible expression of $-

galactosidase in yeast." To understand the metes and bounds conferred by this recitation, we turn to an analysis of claim construction for claim 25 as a whole.

Claim 25, part (i), recites a yeast cell transforming step, and defines the DNAs introduced into yeast cells. Part (i)(a) defines the ligand responsive element. Part (i)(b) defines the receptor. Steps (ii) and (iii) concern inducing expression and recovering protein.

First, construction of part (i)(b). The DNA encoding the receptor has to be under the control of elements providing for expression in yeast. The receptor is a natural nuclear receptor for steroids or retinoids or thyroid hormones or vitamin D3, or is a variant of "said receptors which retain the function of said receptors in yeast." The receptor comprises a first fragment that recognizes the ligand, and a second fragment that binds to the transcriptional control sequence. One point for interpretation is what is meant by "the function of said receptors in yeast." Is "the function of said receptors" to bind the natural ligand-responsive DNA sequence, or is it more broadly to bind any responsive DNA sequence? Since the function of the natural receptor is two-fold, to bind the natural ligand and to bind the natural ligand-responsive element, we interpret "the function" as meaning the function of binding both the natural ligand and the natural ligand-responsive element. This is consistent with the treatment in the specification, which distinguishes between "natural" receptor and "hybrid" or "chimeric" receptor proteins (e.g., page 6, lines 9-16, and 26-27), where an example of the latter has a ligand-binding portion of higher eukaryotic

origin and a DNA-binding portion of yeast origin (page 6, lines 11-16). Therefore, we read the scope of (i)(b) to mean variants which bind both the natural ligand and the natural response element.

Construction of part (i)(a) follows. The response element is a natural ligand responsive element, or a variant which retains the function of a natural ligand responsive element. If a variant, the variant must be a palindromic sequence or a repetition of a palindromic sequence, and the variant "retains the function of a natural ligand responsive element activating sequence in" a specified test. Since a natural ligand responsive element functions by binding with the natural receptor, we read this part of the claim as meaning variants which bind the same receptor as the natural sequence.

We note that the state of the art includes knowledge of methods to test for the functionality of variations from the sequence of a natural ligand responsive element. See for example the Martinez publication cited by the examiner. Martinez also indicates that there was knowledge in the art of the responsive elements for a number of different steroids, recognition of the structure of a consensus sequence in the natural structure of glucocorticoid-responsive elements, and some knowledge of the sequence structure necessary for the specificity of the response element. The examiner's statement of the rejection is devoid of analysis of the state of the prior art. Although the "variants" recited in the claim are defined using functional language, there is nothing inherently wrong with functional language. Persons of ordinary skill of the art had knowledge of the structure of

some operative variants of ligand-responsive elements (e.g. Martinez), and of routine methods of sequence variation and functional assay for induction of $-galactosidase activity under the control of the test DNA element or the test receptor protein variant. Therefore, we do not find that those of skill in the art were, at the time of the invention, unable to determine the metes and bounds for variants of a natural higher eukaryotic steroid, retinoid, thyroid hormone, or vitamin D3 receptor proteins which retain the functions of a natural steroid, retinoid, thyroid hormone, or vitamin D3 receptor protein in yeast. Similarly, we conclude that those of skill in the art were able to determine the metes and bounds for a variant of a higher eukaryotic natural ligand responsive element that is palindromic (or a repetition of a palindromic sequence) that retains the function of a natural ligand responsive element.

In regard to the orientation of repeated elements to each other and to the other elements of the construct, we note the following. In the molecular biology art, the term "direct repeat" is defined as "Identical or closely related nucleotide sequences present in two or more copies in the same orientation within the same molecule".[3] Therefore the recitation "directly repeated" in claim 27 does indicate the orientation of the repeated elements to each other. In regard to the orientation of the repeated response elements to other elements of the construct, we agree that the claim does not specify how the elements are oriented with regard to the foreign protein coding sequence. However, this does not

[3]McGraw-Hill Dictionary of Scientific and Technical terms, fifth edition.

render the claim indefinite. At best it may raise a question of enablement. However, even if some of the possible orientations were inoperative, the claims are not necessarily invalid. "It is not a function of the claims to specifically exclude . . . possible inoperative substances...".[4]

We therefore conclude that, when read in light of the specification and in light of the teachings of the prior art, the claims are not indefinite.

Obviousness

Before a conclusion of obviousness may be made based on a combination of references, there must have been a reason, suggestion, or motivation to lead an inventor to combine those references. Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996) (citation omitted). Moreover, the prior art must also establish that one would have had a reasonable expectation of achieving the present invention, i.e., a reasonable expectation of success. In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be found in the prior art, not in appellants' disclosure. In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

[4] Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1576-77, 224 USPQ 409, 414 (Fed. Cir. 1984).

The claims are rejected as unpatentable over Cushing taken with Evans and a number of additional references. The additional references deal with variations of the estrogen receptor protein, variations of the estrogen response element, genetic engineering methods or assays, and with use of protease deficient yeast. Cushing teaches culturing yeast in the presence of estradiol. Evans teaches, among many other things, a process for controlling the expression of a heterologous protein using a hormone responsive transcriptional control unit very similar to the control method recited in appellants' claims. Evans mentions yeast exactly once in the >40-page patent disclosure, in column 10, lines 52-54, in the "Summary of the Invention." The summary starts with statements regarding DNAs encoding proteins which have the hormone-binding and/or transcription-activating properties characteristic of a glucocorticoid receptor, a mineralocorticoid receptor, or a thyroid hormone receptor. After several paragraphs dealing with the nucleic acid coding sequence, Evans states that the invention comprises a cell, preferably a mammalian cell, transformed with a DNA of the invention, expressing the receptor in a cell. The next paragraph states that the invention comprises cells, including yeast cells and bacterial cells such as those of E. coli and B. subtitlis, transformed with DNA's of the invention. Five paragraphs later, Evans discusses "methods for producing desired proteins in genetically engineered cells."

We do not agree with the examiner that the single mention of yeast in Evans is sufficient to suggest application of Evan's expression control method to yeast with a

reasonable expectation of success. The Evans disclosure makes no clear link between yeast and the expression control method using hormones and hormone receptor proteins. Even if one skilled in the art were to view the mention of yeast as a suggestion to try expressing a protein in yeast under the control of a hormone-responsive element and a hormone receptor, neither Evans nor Cushing (nor any of the additional references) provides a reasonable expectation of success for the method at the time the invention was made. None of the references cited in the rejection indicate contemporary recognition in the art for cross-functionality in yeast for higher eukaryotic receptor proteins such as the receptor proteins recited in appellants' claims. Cushing discloses an endogenous estrogen-binding protein in yeast and an endogenous estradiol-like product. The teachings of Cushing do not lead to a reasonable expectation of success, as it was unknown if the yeast estrogen-binding protein functioned in the same manner as the mammalian estrogen receptor. Indeed, one of ordinary skill in the art might have reasonably expected the endogenous estrogen-binding protein in yeast to compete with or interfere with the binding of estrogen to the recombinant estrogen receptor, or expected the endogenous estradiol-like compound to act as an undesired inducer. Therefore, we see the invention as obvious to try at best, in view of the combined teachings of the references. That is not a proper standard of obviousness. In re O'Farrell, 853 F. 2d 894, 904, 7 USPQ2d 1673, 1681(Fed. Cir. 1988).

REVERSED

Sherman D. Winters	)
Administrative Patent Judge	)
	)
	)
	) BOARD OF PATENT
William F. Smith	)
Administrative Patent Judge	) APPEALS AND
	)
	) INTERFERENCES
	)
Toni Scheiner	)
Administrative Patent Judge	)

Kendrew H. Colton
Fitch, Even, Tabin & Flannery
1801 K Street, NW
Washington, DC 20006

WS/dym